THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 33

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte CHRISTINA K. EDDY

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Appeal No. 1995-2772
Application 08/001,063

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ON BRIEF

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Before WILLIAM F. SMITH, ELLIS, and ROBINSON, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 44 through 55, 57, 58, 68 through 73, 76, 77, 79 and 80, all the claims remaining in the application. Claims 1 through 43, 56, 59 through 67, 74, 75, 78 and 81 through 90 have been canceled.

Claim 44 is illustrative of the subject matter on appeal and reads as follows:

44. A biotin overproducing recombinant cell transformed with an Escherichia coli bioH gene, said recombinant cell being capable of producing more biotin than a cell not transformed with an Escherichia coli bioH gene.

The references relied upon by the examiner are:

Gloeckler et al. (Gloeckler)	5,096,823	Mar. 17, 1992 (effective filing date Sep. 30, 1987)
Fisher	5,110,731	May 5, 1992 (effective filing date Jun. 13, 1990)
Baker et al. (Baker)	5,212,058	May 18, 1993 (effective filing date Nov. 08, 1991)

O'Regan et al. (O'Regan), "Nucleotide sequence of the bioH gene of Escherichia coli," Nucleic Acids Research, Vol. 17, No. 19, p. 8004 (1989).

Singer et al. (Singer), "Phage T4 expression vector: protection from proteolysis," Gene, Vol. 106 pp. 1-6 (1991).

Eur. Patent Application (Speck)	0 379 428	July 25, 1990

The claims stand rejected as follows:[1]

I. Claims 57, 58 and 73 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure.

[1] The rejection of claim 79 under 35 U.S.C. § 112, second paragraph, set forth on page 17 of the Examiner's Answer (Paper No. 21) was withdrawn on p. 2 of the Supplemental Examiner's Answer (Paper No. 29).

II. Claims 44 through 49, 51, 52, 54, 68 through 70, 72, 76, 77, 79 and 80 stand rejected under 35 U.S.C. § 103 as being unpatentable over Fisher, Gloeckler and O'Regan.

III. Claims 53 and 55 stand rejected under 35 U.S.C. § 103 as being unpatentable over Fisher, Gloeckler and O'Regan in view of Speck.

IV. Claims 50 and 71 stand rejected under 35 U.S.C. § 103 as being unpatentable over Fisher, Gloeckler and O'Regan in view of Singer.

V. Claims 57, 58 and 73 stand rejected under 35 U.S.C. § 103 as being unpatentable over Fisher, Gloeckler, O'Regan and Singer in view of Baker.

We have carefully reviewed the entire record which includes, inter alia, the specification, the appellant's main Brief (Paper No. 20), Reply Brief, (Paper No. 26) and second Reply Brief (Paper No. 30), the Examiner's Answer (Paper No. 21) and Supplemental Answer (Paper No. 29), as well as the Declaration of Mr. Campbell (Paper No. 13), and we find ourselves in agreement with the appellants' position with respect to the rejections under 35 U.S.C. § 103. Accordingly, we reverse Rejections II through V.

As to Rejection I, we note the appellant's statement on p. 4 of the main Brief, that a deposit will be made of pDIP18 plasmid, on or before the date of payment of the issue fee, as required by 37 C.F.R. § 1.809. The examiner acknowledges this statement, but for

reasons which are not clear to us, failed to withdraw the rejection. Supplemental Answer, Paper No. 29, p. 3. Since there is no controversy as to this issue, we consider the rejection as being MOOT.

Discussion

Biotin, also known as vitamin H, is an essential component in the metabolism of most organisms. Specification, p. 1. At the time of the invention, the biotin biosynthetic pathway in Escherichia coli (hereinafter, E. coli) was known to involve at least six enzymes which are encoded by the bioA, bioB, bioF, bioC and bioD genes. Fisher, col. 3, lines 2-4. As indicated by the claim above, the present invention is directed to host cells which are transformed with the E. coli bioH gene and which are capable of producing more biotin than host cells which have not been transformed with the gene. In addition, the invention encompasses recombinant molecules comprising the E. coli bioH gene; methods of increasing biotin production by transforming host cells with said gene; and methods of making said host cells. Useful host cells are said to include bacteria of the genera Escherichia, Bacillus, Pseudomonas, Salmonella, and Corynebacterium, as well as yeast of the genus Saccharomyces. Specification, p. 35.

All of the claims on appeal require a biotin-producing recombinant cell which has been transformed with an E. coli bioH gene such that said cell produces more biotin than a

cell which has not been transformed with said gene.[2] This issue is also at the core of all four rejections under 35 U.S.C. § 103. Thus, there is one issue which is dispositive of this appeal. That is, the correctness of all the rejections hinges on a determination of whether it would have been obvious to one of ordinary skill in the art to construct a biotin overproducing recombinant cell by transforming said cell with an E. coli bioH gene in view of O'Regan and Fisher.[3] From another perspective, the

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[2] We note that claims 68 through 73 are directed to a recombinant molecule comprising an E. coli bioH gene which is operatively-linked to a transcription control sequence. Thus, technically speaking these claims do not require a recombinant host cell having the referenced biotin-producing characteristics. However, the sole reason provided by the examiner as to why it would have been obvious to one of ordinary skill in the art to transform a host cell with an E. coli bioH gene which has been placed under the control of a suitable promoter (e.g., claim 68) is to increase the yield of biotin in a recombinant host cell. Answer, p. 12. Since the examiner has not provided any evidence to support the reason, and from our discussion it is apparent that we find the evidence of record to be to the contrary, we have considered these claims as being on the same footing as all the others. That is, in view of the examiner's statement of the rejection, the patentability of these claims, like that of all the others, hinges on whether it would have been obvious to those having ordinary skill in the art that an E. coli bioH gene which is operatively linked to transcription control sequences and expressed in a host cell would result in a host cell capable of producing more biotin than a host cell which has not been transformed with said gene.

[3] We recognize that the examiner has also relied on Gloeckler, a reference which, inter alia, discloses complementing a bioH E. coli mutant with a plasmid comprising a DNA encoding the Bacillus sphaericus bioF, bioW and bioX genes.
Col. 12, lines 39-40; Figures 22 and 23. This reference was applied in the first Office action against the original claim 44 which encompassed an E. coli bioH gene or a "functional equivalent thereof." The phrase "functional equivalent thereof" was removed by amendments filed by the appellant in Paper Nos. 10 and 14. In our view, the examiner
(continued...)

dispositive issue here is whether it would have been obvious to a person of ordinary skill in the art that the transformation of a host cell with an E. coli bioH gene and the expression of the gene therein, would result in the production of a recombinant cell capable of producing more biotin than a host cell not transformed with said gene and would said person have had a "reasonable expectation of success" in producing such a recombinant cell? In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); In re O'Farrell, 853 F.2d 894, 903-04, 2 USPQ2d 1673, 1681 (Fed. Cir. 1988).

The prior art relied upon by the examiner establishes that (i) the biotin biosynthetic pathway was partially characterized, and (ii) the starting materials and the methods used for transforming host cells and expressing heterologous gene products therein, were well known at the time of the present invention. For example, as discussed above, it was known in the art that in E. coli the biotin synthetic pathway involved at least six (6) enzymes which are encoded by the bioA, bioB, bioF, bioC, bioD and bioH genes. Fisher, col. 3, lines 2-4. The E. coli bioA, bioB, bioD and bioF genes were characterized and were known to encode "7, 8-diaminopelargonic acid aminotransferase (also called 7, 8-diaminopelargonic acid synthase), biotin synthetase (also called biotin synthase),

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[3](...continued)
should have taken a step back and re-evaluated the relevance of Gloeckler after claim 44 was amended to its present form. Now, we find that the reference only obfuscates the relevant issues in this case.

desthiobiotin synthetase (also called desthiobiotin synthase), and 7-keto-8-aminopelargonic acid synthetase (also called 7-keto-8-aminopelargonic acid synthase)." Specification, p. 2; see also, Fisher, col. 3, lines 4-6. Prior art investigators demonstrated that biotin could be produced in a biotin retention-deficient E. coli host cell by transforming said E. coli host cell with a plasmid comprising the DNA encoding the biotin gene cluster bioA, bioB, bioF, bioC and bioD. Fisher, the abstract, and Examples 1, 2 and 5[4] through 7. Furthermore, at the time of the present invention, we find that the applied prior art establishes that the complete nucleotide sequence of the E. coli bioH gene and the amino acid sequence of the protein which it encodes were known. O'Regan, p. 8004. It was also understood that the E. coli bioH gene product was an essential component of the biotin biosynthetic pathway. Fisher, col. 3, lines 14-15. However, what was not known or understood in the art at the time of the present invention was the function of the E. coli bioH gene product or the role it played in the biotin biosynthetic pathway. Specification, para. bridging pp. 2-3; Fisher, col. 3, lines 9-14; O'Regan, p. 8004, lines 1-3.

Accordingly, the issue which must be resolved is whether at the time of the invention would a hypothetical person having ordinary skill in this art have performed this seemingly obvious task of expressing the E. coli bioH gene in a host cell and would it have been

[4] We note that Fisher has two examples which are denominated Example 5. We refer to the second Example 5 which is in col. 8.

obvious to said person that the transformation of a host cell with said gene would result in the production of a cell capable of making more biotin than a cell not transformed with said gene, or would this task have been "obvious to try" by said hypothetical person. Our appellate reviewing court distinguished these two situations in In re O'Farrell, 853 F.2d at 903, 7 USPQ2d at 1681 stating:

> The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g., In re Geiger, 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie, 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986), cert. denied, [ ] 107 S.Ct. 1606 [ ] (1987); In re Tomlinson; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The initial burden of establishing a prima facie case of obviousness lies with the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). Here, we find that the examiner has gone to great lengths to explain the teachings of the prior art, and to explain why it would have been obvious to a person having ordinary skill in the art to

transform a host cell and to express therein the E. coli bioH gene and why said persons would have had a reasonable "expectation of success" that the resultant host cell would produce more biotin than a non-transformed host cell. The examiner concludes that it would have been obvious to express the
E. coli bioH gene taught by O'Regan in a host cell in order to increase the yield of biotin synthesis because "the bioH gene was the only remaining gene known to be present in the chromosome of E. coli that was identified by all working in the field as contributing an enzymatic activity to the biosynthesis of biotin." Answer, p. 12. The examiner contends that "the biotin synthesis method of Fisher would clearly have provided one of ordinary skill in the art at the time the invention was made with the means for increasing the gene dosage of the only gene not present in the transcriptional units used by Fisher." Id., p. 13. The examiner summarizes his position by stating that "In short, placing the bioH gene in an expression context equivalent to that of Fisher was the only available improvement on the method of Fisher once its coding sequence was disclosed by O'Regan et al." [Emphasis added]. Id.

In our view, the examiner has presented a classic "obvious to try" argument as to why the claimed invention would have been obvious to those of ordinary skill in the art. Here, the examiner recognizes that the nucleotide sequence of the E. coli bioH gene was known in the art and, therefore, the next logical research step was to express the gene in a

host cell. However, we find that the examiner is confusing the level of skill in the art with the teachings of the prior art. In re Kratz, 592 F.2d 1169, 1175, 201 USPQ 71, 76 (CCPA 1979)("[T]here is a difference between somehow substituting skill in the art for statutory prior art, as the PTO attempts to do here, and using that skill to interpret the prior art"). That is, although numerous facts were known in the art about biotin biosynthesis, as discussed above, a critical fact the examiner has overlooked is that the function of the E. coli bioH gene product in the biosynthetic pathway was not known at the time the invention was made. Specification, para. bridging pp. 2-3; Fisher, col. 3, lines 9-14; O'Regan, p. 8004, lines 1-3. For example, O'Regan discloses

> The exact nature of the early steps of the biotin biosynthetic pathway of E. coli remains a mystery. Both the bioH and bioC gene products have been shown to be implicated in these early steps but their precise function is unknown.

Thus, while the disclosure of the complete nucleotide sequence of the E. coli bioH gene by O'Regan might have made the transformation of a host cell with the gene and its expression therein enticing to those of ordinary skill in the art "to try," in this case, this is not sufficient to establish a prima facie case of obviousness. In re Eli Lily & Co., 902 F.2d, 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990)("An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that

further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.")

The proper approach to obviousness must take the claimed invention "as a whole" into account. Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1566-68, 1 USPQ2d 1593, 1595-97 (Fed. Cir.), cert. denied, 481 U.S. 1052 (1987); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1539, 218 USPQ 871, 879 (Fed Cir. 1983). Here, the invention as a whole requires that the examiner establish that it would have been obvious to one of ordinary skill in the art that a recombinant host transformed with the E. coli bioH gene would be capable of producing more biotin than a cell which is not transformed with the gene. Because the evidence of record establishes that the function of the bioH gene was not known, it reasonably follows that it would not have been obvious to those of ordinary skill that the expression of the E. coli bioH gene in a host cell would result in the production of a recombinant cell having the claimed characteristics.

We acknowledge the examiner's arguments that those skilled in the art would have had a reasonable expectation of success in improving biotin yields based on Gloeckler's disclosure that the B. sphaericus bioF, bioW and bioX genes "allowed E. coli mutants deficient in the activity of the bioH gene to utilize pimelate as the precursor for biotin biosynthesis. ... [and because] ... Gloeckler et al. teach their opinion that the bioH

gene is regulated in common with the distant bioA, bioB, bioC, bioD and bioF genes of the E. coli biotin operon by the repressor product of the bioR gene.... "

Id. We point out, however, that in determining obviousness there is more than one criterion which must be considered. It must be determined whether (i) the prior art would have suggested the claimed invention, and (ii) those of ordinary skill in the art would have a "reasonable expectation of success" in achieving the claimed results. In re Vaeck, 947 F.2d at 493, 20 USPQ2d at 1442 (Fed. Cir. 1991); In re Dow Chem., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988); In re O'Farrell, supra. Since the examiner has not established the former criterion, we need not reach the merits of these secondary arguments. Moreover, as we pointed out in footnote 3, above, we do not find the teachings of Gloeckler to be of particular relevance to the invention as now claimed.

In view of the foregoing, Rejection II is reversed.

As discussed above, we have considered all the claims as containing the limitation that the recombinant host cell transformed with an E. coli bioH gene be capable of producing more biotin than a cell not transformed with said gene. Since we do not find that this limitation is suggested by Fisher, Gloeckler and O'Regan, we cannot sustain the examiner's rejections of dependent claims 50, 55, 53, 57, 58, 71 and 73 over the additional prior art of Speck, Singer and Baker. That is to say, the obviousness of the

common limitation has not been established by the examiner using the three primary references, and we do not find that the additional references provide any teachings that would have rendered the claims of Rejections II, IV and V unpatentable under 35 U.S.C. § 103. Accordingly, Rejections II, IV and V are reversed.

REVERSED

William F. Smith)
Administrative Patent Judge)
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)
Joan Ellis) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES
)
)
)
Douglas W. Robinson)
Administrative Patent Judge)

Melissa A. Shaw
Whyte, Hirschboeck & Dudek, S.C.
111 East Wisconsin Avenue
Suite 2100
Milwaukee, WI 53202

JE/cam